REMARKS

In the Decision on Appeal dated January 30, 2008, the Board of Patent Appeals and Interferences ("the Board") indicated that the instant application could be further prosecuted by requesting that prosecution be reopened by submitting an amendment or evidence or both under 37 C.F.R. § 41.50(b)(1) or requesting rehearing under 37 C.F.R. § 41.50(b)(2). (Decision at 54.) Applicant chooses to proceed by requesting that prosecution be reopened by submitting an amendment and evidence under 37 C.F.R. § 41.50(b)(1).

Reconsideration of this application is respectfully requested. Claims 152-162 and 164-167 have been canceled, and claim 172 has been amended. Claims to cattle, sheep, pig, and goat species have been canceled in this application without prejudice or disclaimer to obviate a statutory double patenting rejection over co-pending application No. 09/225,233.

REJECTIONS UNDER 35 U.S.C. § 101

In its Decision, the Board affirmed the Examiner's rejection of claims 152-171 under 35 U.S.C. § 101 as being drawn to non-statutory subject matter, albeit as a NEW GROUND OF REJECTION. (At 16.) The Board characterized the issue with the following question: Can it be that a copy of a preexisting thing is patentable subject matter? (*Id.* at 13.)

Applicant traverses the rejection. Although an exact copy of a preexisting thing might not be patentable, the issue in this case is more succinctly phrased as: Is a time-delayed, inexact copy made by man of a pre-existing mammal, which differs in many

ways from the pre-existing mammal, patentable subject matter? When the appropriate legal standard is applied to the facts in this case, the answer is yes.

The Board found that mammals do not naturally reproduce by cloning, and that the argument is very strong that a cloned mammal covered by Applicant's claims is a non-naturally occurring product of human ingenuity. (Decision at 13.) In other words, Applicant is not claiming a product of nature, but one that is made by man. This finding of the Board is sufficient for Applicant's claims to fulfill the requirements of 35 U.S.C. § 101.

As the Supreme Court held in *Diamond v. Chakrabarty*, statutory subject matter includes "anything under the sun that is made by man." 447 U. S. 303, 308 (1980). The relevant distinction between non-statutory and statutory subject matter is between products of nature, whether living or not, and human-made inventions. *Id*. at 313. Since clones of mammals are not products of nature, but are human-made inventions, the requirements of 35 U.S.C. § 101 are fulfilled by Applicant's claims.

Despite the Board finding that there is a very strong argument that Applicant's clones are non-naturally occurring products of human ingenuity, the Board nevertheless went on to find that this was insufficient to fulfill the requirements of 35 U.S.C. § 101. (Decision at 13.) The Board stated that "the term 'new' in § 101 cannot be ignored." (*Id*.) The Board asked: "[W]hat limitations of claims distinguish the claimed product (a clone of a specified mammal) from other mammals of that type – in particular, from the donor of the nucleus?" (*Id*.)

The term "new" in § 101 has not been ignored. Rather, the issue of whether an invention is "new" within the context of 35 U.S.C. § 101 is answered by answering

whether the invention is a non-naturally occurring product of human ingenuity. If it is non-natural and made by man, it is "new." *See* 447 U. S. at 308. Under this analysis, Applicant's clone is "new" because it does not exist in nature, but is made by man. Nothing further should have been required.

Nonetheless, to assess "newness," the Board indicated that the term "new" in 35 U.S.C. § 101 is to be defined in accordance with the provisions of 35 U.S.C. § 102 (at 9) and compared Applicant's claimed clone to its parent under an anticipation analysis. The Board admitted that the clone "will not be an exact copy of the 'parent.'" (Decision at 14.) The Board conceded that environmental factors will result in physical differences between the clone and its parent. (*Id.*) The Board further admitted that the clone and its parent will occupy a different space and time and will have phenotypic differences. (*Id.* at 15.) These differences are sufficient to negate a finding of anticipation of a clone by its parent under the proper legal analysis.

Anticipation under 35 U.S.C § 102 can be found only when the reference discloses ***exactly*** what is claimed; where there are differences between the reference disclosure and the claim, the rejection must be based on 35 U.S.C § 103, which takes differences into account. *Titanium Metals Corp. v. Banner*, 227 USPQ2d 773, 777 (Fed. Cir. 1985). Thus, anticipation is not shown by a prior art disclosure which is only "substantially the same" as the claimed invention. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253, 256 (Fed. Cir. 1985). Rather, the ***identical*** invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Following legal precedent, the fact that the clone and its parent are different, which the Board concedes, precludes anticipation of Applicant's claims. As explained by the Court of Appeals for the Federal Circuit in overturning an anticipation rejection where there were differences between the claims and the prior art:

> The opinion says anticipation may be shown by less than "complete anticipation" if one of ordinary skill may in reliance on the prior art "complete the work required for the invention", and that "it is sufficient for an anticipation 'if the general aspects are the same and the differences in minor matters is only such as would suggest itself to one of ordinary skill in the art.'" Those statements relate to obviousness, not anticipation. Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim. *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 960, 148 USPQ 298, 301 (Ct. Cl. 1966). A prior art disclosure that "almost" meets that standard may render the claim invalid under §103; it does not "anticipate."

Connell et al. v. Sears, Roebuck & Co., 220 USPQ 193, 198 (1983).

Although the Board conceded that a clone and its parent will have many differences, the Board dismisses these differences as "trivial." First, the Board found the fact that the clones occupy a different space and time from the parent "trivial," and that this difference is true of any two objects, one of which is a copy of the other. (Decision at 15.) Next, the Board found that the phenotypic differences due to environment are similarly trivial in that any pair of mammals will look and behave somewhat differently, and that any two macroscopic objects will not be completely identical on some scale. (*Id.*) The Board concluded that such trivial and uncontrollable differences cannot be the basis of differences that result in patentable distinctness. (*Id.*) The Board concluded that the clones are not "new" under 35 U.S.C. § 101 because it is not apparent what limitations of the claims distinguish (in the anticipation sense) the clone from the donor. (*Id.* at 15-16.)

The Board's conclusions are contrary to established legal precedent. Legal precedent clearly dictates that any difference, trivial or otherwise, precludes anticipation. See *Connell*, 220 USPQ at 198. Any differences must be assessed under an obviousness analysis, which the Board did not perform and which should have no relevance to whether Applicant's clones are patentable subject matter under 35 U.S.C. § 101.

Since Applicant's clones are non-naturally occurring products of human ingenuity, and they cannot be anticipated by their parents, Applicant's claims are unquestionably statutory subject matter under 35 U.S.C. § 101.

In its Decision, the Board conflates anticipation and obviousness:

> We must therefore ask, what limitations of the claims distinguish the claimed product (a clone of a specified animal) from other mammal of that type – in particular, from the donor of the nucleus? In answering this question, we must bear in mind that, as discussed in more detail in the next section, product-by-process claims are claims to the product itself, and are anticipated by the prior description of any product, no matter how made, that is the same as, or substantially the same as, a product made by the recited process.

(Decision at 13.) Although a claim may be anticipated by the prior description of the ***same*** product, no matter how made, it cannot be anticipated by a product that is only ***substantially the same*** as the claimed product. *Jamesbury*, 225 USPQ at 256 ("anticipation is not shown by a prior art disclosure which is only 'substantially the same' as the claimed invention.").

Applicant further notes that claims 152-162, which were product-by-process claims, have been canceled. Pending claims 163 and 168-171 are product claims that do not recite any process limitations. The pending claims recite that the mammal is a **clone** of a pre-existing, non-embryonic donor mammal. It is irrefutable that nature does

not make **clones**. Since clones of pre-existing mammals do not exist in nature, the clones must be new. Thus, the clones of claims 163 and 168-171 are statutory subject matter.

Although the PTO may be correct, under *In re Best*, in shifting the burden to Applicant to show that the parental donor mammals and claimed clones are different. Applicant has fulfilled this burden by providing evidence that the claimed clones and their parents are different. (*See* previously submitted Declaration of David Wells.) As additional evidence, Applicant provides herewith a Declaration of Irina A. Polejaeva, Ph.D., explaining many of the differences between the parental donor mammals and claimed mammals. (Declaration at ¶¶88-106.)

Applicant's previously submitted evidence appears to have been sufficient to fulfill Applicant's burden since the Board conceded that the parental donor mammals and claimed mammals are different in many ways. (Decision at 14-15.) Applicant's new evidence serves as further proof. Whether these differences between Applicant's clone and its parent are "trivial" or are sufficient for patentability is not an issue under 35 U.S.C. § 101 or 35 U.S.C. § 102, but rather an issue under 35 U.S.C. § 103. *See Connell*, 220 USPQ at 198.

Statutory Double Patenting (§ 101)

In its Decision, the Board affirmed the Examiner's rejection of claims 152-171 under 35 U.S.C. § 101 as not being patentable over the claims of U.S. Application No. 09/225,233. (Decision at 20.) The Board alleged that the only differences between the claims are in the source of the donor nuclei and the details of the recited process of somatic cell nuclear transfer. (*Id*. at 19.) The Board concluded that Applicant has not

argued that a mammal cloned from a fetal cell is different from a mammal cloned from a more developed cell in any ***substantive*** way. (*Id.*)

Applicant traverses the rejection. Although a clone of a non-embryonic, donor mammal **can** be a clone of a fetal donor mammal, a clone of a non-fetal, non-embryonic, donor mammal **cannot** be a clone of a fetal mammal. A clone of a **fetal** donor mammal would not infringe the claim limited to a clone of a **non-fetal**, non-embryonic, donor mammal. Thus, the test enunciated in *Vogel* demonstrates that Applicant was not claiming the identical invention twice. *See In re Vogel*, 422 F.2d 438, 441 (CCPA 1970).

Nevertheless, pending claims 163 and 168-171 do not recite sheep, cattle, goat, or pig species. Claims to sheep, cattle, goat, and pig species are being pursued in co-pending application No. 09/225,233. The pending claims in co-pending application No. 09/225,233 have also been amended to eliminate recitation of mouse, rabbit, horse, and rat species. Thus, the two applications, as amended, do not recite the same species, and cannot be claiming the identical invention. Accordingly, Applicant respectfully requests withdrawal of the rejection.

REJECTIONS UNDER 35 U.S.C. §§ 102/103

In its Decision, the Board affirmed the Examiner's rejection of claims 152-160, and 163-169 under 35 U.S.C. § 102 or § 103, but reversed the Examiner's rejection of claims 152-154, 161-163, and 170-171 under 35 U.S.C. § 102 or § 103. (Decision at 53-54.) The Board groups the rejections into two categories: those that relied on prior art disclosing clones made using embryonic nuclear transfer procedures (Class 1) and

those that relied on prior art disclosing sexually reproduced mammals, namely, horses and rats (Class 2). (Decision at 20-23.)

The Board concluded that the claims of Class 2 (horses and rats) were not anticipated because the "nuclear donor" genome is not identical to that of the clone, because the genetic complement of a sexually reproduced mammal is only 50% identical with that of either one of its parents. (*Id*. at 27.)

However, the Board concluded that the claims of Class 1 were anticipated by clones prepared by other techniques, citing Sims et al. (1994), McLaughlin et al. (1990), Prather et al. (1989), Yong et al. (1991), Cheong et al. (1993), and Yang et al. (1992). (*Id*. at 26.) The Board argued that Applicant did not direct its attention to any evidence or argument of record that the clones produced by the *processes recited* in the appealed claims differ from clones produced by the processes described in the cited references. (*Id*.) Applicant traverses the rejection.

Applicant notes that claims 152-162, which were product-by-process claims, have been canceled. New claims 163 and 168-171 are product claims that do not recite any process limitations. New claims 163 and 168-171 recite that the mammal is a clone of a pre-existing, ***non-embryonic*** donor mammal.

Anticipation under 35 U.S.C § 102 can be found only when the reference discloses exactly what is claimed. *Titanium*, 227 USPQ2d at 777. The identical invention must be shown in as complete detail as is contained in the patent claim. *Richardson v. Suzuki Motor Co*., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Thus, anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention. *Connell*, 220 USPQ at 198.

The cited references do not disclose exactly what is claimed. The prior art clones are clones of a donor ***embryo***. Thus, the cited references are missing an element recited in Applicant's claims. These references do not teach or suggest a mammal that is a clone of a pre-existing, ***non-embryonic*** donor mammal. This limitation of Applicant's claim precludes Applicant's clone from being anticipated by the cited references. See *Connell*, 220 USPQ at 198.

The references cited by the Office each describes clones made by embryonic cloning procedures. (Declaration at ¶¶107-146.) That is, these references report a process of cloning using nuclear transfer starting with an embryo as the nuclear donor. (*Id*. at ¶108.) The embryos used as the nuclear donors were generated by normal sexual reproduction. (*Id*. at ¶147.) Thus, these embryos were not identical to either of its parents. (*Id*. at ¶148.) Furthermore, the embryos were destroyed during the embryonic cloning procedures. (*Id*. at ¶149.) Consequently, the embryos used as the nuclear donors in the embryonic cloning procedures of the cited references were never "non-embryonic." (*Id*. at ¶150.)

Furthermore, the non-embryonic parental mammals in the cited references would have been the two parents of each of the embryos used as the nuclear donors in the embryonic cloning procedures. (*Id*. at ¶151.) The embryonic clones made in these references were not clones of either of these parental mammals, since sexual reproduction was used to generate the embryos used in the embryonic cloning procedures. (*Id*. at ¶152.) Rather, these clones would have been a mixture of the genetic complement of their two parents, and thus the clones would not have had the same genetic complement as either of the parents. (*Id*. at ¶153.) Consequently, the

clones generated by the embryonic cloning procedures of the cited references were not a live-born clone of a pre-existing, ***non-embryonic***, donor mammal. (*Id*. at ¶¶154-155.) These prior art references lack this element of Applicant's claims.

A live-born clone of a pre-existing, non-embryonic, donor mammal as claimed is a time-delayed, inexact copy of a non-embryonic mammal. (*Id*. at ¶156.) The claimed clone requires two animals, namely, a pre-existing, non-embryonic, parental mammal and a clone of that parental mammal. The cited references did not generate such a pair of mammals. (*Id*. at ¶157.) In none of the cited references did a pre-existing, non-embryonic, parental mammal and a clone of that parental mammal exist. (*Id*. at ¶158.) The prior art references lack this requirement of Applicant's claims.

Moreover, the embryonic cloning procedures of the cited references preclude even the coexistence of the clone and the donor embryo. (*Id*. at ¶159.) This is due to fact that, in the embryonic cloning procedures of the cited references, the embryonic donor was destroyed during the generation of the clone. (*Id*. at ¶160.) In contrast, a live-born clone of a pre-existing, ***non-embryonic***, donor mammal as claimed can coexist with its non-embryonic donor. (*Id*. at ¶161.) The generation of such a clone does not require destruction of the donor mammal in generating the clone. (*Id*.) The prior art references lack this requirement of Applicant's claims.

Thus, Applicant's clones differ in many ways from the clones of the cited references. These differences preclude a finding of anticipation of Applicant's claims. *See Titanium*, 227 USPQ2d at 777.

The differences between Applicant's clones and the clones of the cited references also preclude a finding of obviousness of Applicant's claims. As explained in M.P.E.P. § 2141.02:

> In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the invention as a whole would have been obvious. *Stratoflex, Inc. v Aeriquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed Cir. 1983); *Schneck v. Norton Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed Cir. 1983).

A live-born clone of a pre-existing, non-embryonic, donor mammal as claimed is not taught or suggested by the cited references. (Declaration at ¶162.) Although the cited references demonstrated that cloned mammals could be made from embryonic nuclear donor cells, it was unexpected that a clone of a non-embryonic donor mammal could be generated prior to Applicant's invention. (Id. at ¶163.)

Prior to Applicant's invention, the generation of a live-born clone of a pre-existing, non-embryonic, donor mammal would have been expected to be impossible. (*Id*. at ¶164.) Since there must be a reasonable expectation of success to support a conclusion of obviousness, what was thought to be impossible cannot be obvious. *See, e.g., In re Rinehart*, 189 USPQ 143 (CCPA 1976). Accordingly, Applicant respectfully requests withdrawal of the rejection.

REJECTIONS UNDER 35 U.S.C. § 112

In its Decision, the Board affirmed the rejection of claims 152-154, 159-163, and 168-171 under 35 USC 112, first paragraph, as lacking an enabling disclosure. (Decision at 54.) Applicant traverses the rejection for the reasons set forth in numerous responses, in Applicant's Appeal Brief, in Applicant's Reply Brief, and in the accompanying Declaration of Irina A. Polejaeva, Ph.D.

The Board concluded that Applicant's claims to mice, rabbits, horses, and rats were not enabled. In its Decision, the Board noted that Applicant's arguments were not supported by a Declaration from one of skill in the art. (*Id*. at 33.)

Applicant provides herewith a Declaration of Irina A. Polejaeva, Ph.D., in support of the enablement of the claimed invention. In her Declaration, Dr. Polejaeva explains that cloning is an inefficient process and a large number of oocytes may need to be reconstructed to achieve success. (*Id*. at ¶¶19-21 and 75-77.) The probability for producing a clone increases proportionally with the number of oocytes reconstructed, but so does the "work effort," as well as the cost. (*Id*. at ¶77.) The challenge for most laboratories in cloning mammals is one of having sufficient manpower and financial resources, since cloning of mammals is an expensive venture. (*Id*.) The reconstruction of many oocytes for some species can involve large amounts of labor, albeit repetitive in nature, and high costs for infrastructure and personnel. (*Id*.)

As Dr. Polejaeva explains, one way to maximize one's limited resources for cloning mammals is to improve the efficiency of the cloning process. (*Id*. at ¶78.) Such improvements in cloning efficiency have been widely reported in the scientific literature, including many articles references herein. (*Id*.) However, these improvements in efficiency are not strictly required for successful cloning using Applicant's invention; an alternative approach is to simply increase the overall number of reconstructed embryos transferred to recipients. (*Id*.)

Dr. Polejaeva further explains that successful clonings of previously-reported cloned species using increased numbers of reconstructed oocytes are not usually reported in publications, because they are not "publication worthy." (*Id*. at ¶79.) These

clonings are simply repeating what was already known. (*Id.*) Dr. Polejaeva concludes that the successful cloning of a mammal is virtually guaranteed by reconstructing a sufficient number of nuclear transfer embryos. (*Id.* at ¶¶80-82.)

In affirming the rejection, the Board first focused on the purported "failures" of groups to clone rats (Fitchev), rabbits (Renard), and pigs (Prather & Nagashima). The failures of some groups to clone mammals does not equate with a lack of enablement. First, if the group did not follow the teachings of Campbell's '862 application, the fact they failed to clone mammals is irrelevant to enablement. The techniques used by Renard, Prather, and Nagashima are not detailed; therefore, it is not possible to draw any conclusions on enablement from their "failures."

Moreover, as explained by Dr. Polejaeva, the failure in the ability of some laboratories to clone pigs between 1997 and 2000 was likely due to these laboratories reconstructing and/or implanting insufficient embryos to maintain pregnancy. (*Id.* at ¶87.) These failures could have been remedied by reconstructing and transferring more nuclear transfer embryos to each surrogate pig. (*Id.*)

Fitchev is a good example of not reconstructing and transferring sufficient embryos to ensure success. Fitchev et al. (1999) states: "The reconstituted oocytes were placed in the reproductive tract of surrogate mothers for further development but at this time none have be successfully recovered (Table 3)." (At 1528, col. 1, first full paragraph.) Table 3 of Fitchev et al. (1999) shows that "0/5" embryos were recovered from the surrogates. (At 1528, Table 3.) Thus, Fitchev appears to have only transferred 5 nuclear transfer-derived embryos to surrogates. Since only a small percentage of reconstructed embryos actually develop into a live-born mammal, the

inability of Fitchev to clone rats may be due to not transferring enough reconstructed embryos to assure success. Using such low numbers of transferred embryos, the lack of any live births is not surprising.

Successful Cloning of Mice

The Board contended that mice could not be cloned until Wakayama resorted to delayed activation. (Decision at 45.) The Board gave great weight to Wakayama's statement that delayed activation "seems paradoxical after earlier work." (*Id.* at 47.) The Board overlooks the express teachings of the specification to use delayed activation. Applicant's specification, on page 12, line 30, through page 13, line 3, describes using a "delayed activation" procedure for somatic cell cloning:

> Subsequently, the fused reconstructed embryo, which is generally returned to the maturation medium, is maintained without being activated so that the donor nucleus is exposed to the recipient cytoplasm for a period of time sufficient to allow the reconstructed embryo to become capable, eventually, of giving rise to a live birth (preferably of a fertile offspring).
>
> The optimum period of time before activation varies from species to species and can readily be determined by experimentation. For cattle, a period of from 6 to 20 hours is appropriate. The time period should probably not be less than that which will allow chromosome formation, and it should not be so long either that the couplet activates spontaneously or, in extreme cases that it dies.

Wakayama states: "Examination of enucleated oocytes injected with cumulus nuclei revealed that chromosome condensation had occurred within 1 hour of injection (Fig 1b, c)." (Wakayama et al. (1998) at 370, col. 2.) Wakayama indicates that the reconstructed oocytes were activated after chromosome condensation occurred since "chromosome condensation had occurred within 1 hour of injection" and activation occurred at between 1 and 6 hours after injection. (*Id.* at 370, col. 2, and at 371, Table

3.) Thus, Wakayama used a time period that was not less than that which allowed chromosome formation (i.e., condensation) and not be so long either that the couplet activates spontaneously or dies, as taught by Campbell. Wakayama's delayed activation procedure is described in Applicant's specification.

Moreover, Ogura et al. (2000), which is submitted herewith, discusses the technical aspects of cloning mice in Wakayama et al. and contrasts these with the successful cloning of mice by others. (At 57-58.) Ogura concludes that only delayed activation, which is taught by Campbell, is important for cloning mice. Ogura et al. (2000) discusses 4 "key technical points" of Wakayama's paper and concludes that only complete condensation of the donor chromosomes before oocyte activation is important for successful mouse cloning. (*Id*.) This "key technical point" is disclosed by Campbell. That is, the Campbell '862 application teaches that condensation of the donor chromosomes can be induced before oocyte activation. (Specification at 12-13.)

Successful Cloning of Rabbits

The Board contended that the cloning of rabbits required marked asynchrony. (Decision at 46.) The Board dismissed the teachings of Landa and Al-Hasani, explaining that there was no indication that these papers would have been recognized by the skilled artisan as useful for cloning rabbits. (*Id*. at 48.) These papers teach that using asynchronous transfer for *in vitro* manipulated rabbit embryos is beneficial.

The Board overlooked the explicit teachings of Chesné et al. (2002), which indicate that it would have been important for the skilled artisan to take into account physiological features of rabbit embryos from the work of others: "Our work indicates that cloning can probably be carried out successfully in any mammalian species by

taking into account physiological features of their oocytes and embryos." (*Id.*) Thus, as Chesné did, the skilled artisan would have recognized the importance of looking to work by others regarding the transfer of *in vitro* manipulated embryos to host rabbits.

Accordingly, the skilled artisan would have considered the work of Landa (1981) and Al-Hasani et al. (1986) important with respect to *in vitro* manipulated rabbit embryos. Having read these articles, the skilled artisan would have known that using asynchronous transfer for reconstructed rabbit nuclear transfer embryos would be beneficial since reconstructed rabbit nuclear transfer embryos are *in vitro* manipulated embryos.

Successful Cloning of Rats

The Board contended that the cloning of rats required the development of a one-step procedure and the use of a protease inhibitor to address the rapid activation of rat oocytes. (Decision at 46.) The Board alleged that Applicant did not indicate where the problem and solution could be found in the specification or prior art. (*Id.*)

The problem and the solution to spontaneous activation of rat oocytes were well-known in the art. Keefer et al. (1982), which is submitted herewith, reported a problem with rat oocytes, namely, that ovulated rat oocytes activated spontaneously during *in vitro* culture. (At 371, Abstract.) Only 1.3% of rat oocytes remained in metaphase II after *in vitro* culture for 4-5 hours. (*Id.* at 373, Table 1.) Moreover, spontaneous activation of rat oocytes was completed within 90 minutes during *in vitro* culture. (*Id.* at 376-377, bridging paragraph.)

Keefer et al. (1982) also provided a solution to this problem. 98% of rat oocytes remained in metaphase II after *in vitro* culture for 10 minutes, but only 24% after *in vitro*

culture for 25 minutes. (*Id.* at 371, abstract.) Moreover, nearly 75% of rat oocytes remained in metaphase II after *in vitro* culture for 4-5 hours when removed and cultured as rapidly as possible. (*Id.*)

Based on the Campbell '862 application and Keefer et al., it would have been understood in February of 1997 that to obtain rat oocytes in the metaphase II phase of the cell cycle for nuclear transfer, one should try to avoid spontaneous activation of the rat oocytes. Moreover, based on Keefer et al. (1982), it would have been understood that rat oocytes should be removed and cultured as rapidly as possible to avoid spontaneous activation.

Successful Cloning of Horses

The Board contended that the cloning of horses was "aided" by four publications in 2002/2003 that describe various oocyte preparation and activation protocols for horse oocytes, and that without some detailed explanation, it was unlikely that cloning horses was possible without undue experimentation. Great weight was given to the amount of time that passed before a horse was cloned. (Decision at 46-47.)

The amount of time that passed prior to cloning a horse does not equate with a lack of enablement. Cloning is an expensive proposition that requires many resources. (Declaration at ¶77.) Without knowing when the cloning of horses was first attempted, the year in which a horse was first cloned does not inform as to the enablement of the cloning horses.

Moreover, the availability of oocytes appears to be a major factor in horse cloning. Lagutina et al. (2005), a copy of which is provided herewith, states: "In horse nuclear transfer, the availability of horse oocytes is a limiting factor due to the anatomy

and physiology of the mare's ovary which makes this species a poor oocyte donor compared with other large domestic species." (At 560, col. 1, first full paragraph.) Lagutina et al. (2005) further states: "The objectives of our research concentrate on the optimization of the nuclear transfer procedure to make efficient use of the limited numbers of oocytes available in this species." (At 560, col. 1, second paragraph.)

In order to perform nuclear transfer in horses, a source of a large number of horse oocytes is a facilitating factor. That is, the larger the number of oocytes one starts with, the higher the chances of successful generation of cloned horses. However, the low availability of horse oocytes does not equate with a lack of enablement.

To support the rejection of claims to horses, the Board relies on a report by Galli et al. (2003) that cites four publications as having "aided" the successful cloning of horses. (Decision at 43-44 and 47.) The passage in Galli et al. relied on by the Board contains references to inhibiting both protein synthesis and phosphorylation at the oocyte activation stage and using a zona-free manipulation technique. However, neither of these techniques is critical for cloning horses.

First, inhibiting both protein synthesis and phosphorylation at the oocyte activation stage is not critical to successfully clone horses. Hinrichs et al. (1995), a copy of which is provided herewith, indicates that the combination of a calcium ionophore with cycloheximide (CHX), a protein synthesis inhibitor, resulted in 49% activation of equine oocytes. (At 324, first full paragraph.) This experiment was performed *in the absence of any phosphorylation inhibitor*. Thus, it was well-known prior to February of 1997 that the combination of a calcium ionophore with a protein synthesis inhibitor was sufficient for activating horse oocytes. Based on Hinrichs et al.

(1995), it would have been expected in February of 1997 that the combination of calcium ionophore with CHX would serve as to activate nearly half of the equine oocytes exposed to this activation protocol, *in the absence of any phosphorylation inhibitor*. This activation procedure would have been expected to be sufficient to clone horses by somatic cell nuclear transfer in February of 1997.

Likewise, Lazzari et al. (2002) indicates that, for equine oocytes, the activation rate was 30.6% for CHX alone, 60% for 6-dimethylaminopurine (6-DMAP), a phosphorylation inhibitor, and 93.1% for CHX +DMAP. Thus, the activation of equine oocytes in Lazzari et al. (2002) was successful when oocytes were activated first with ionomycin, a calcium ionophore, and second with a protein synthesis inhibitor alone, a phosphorylation inhibitor alone, or with both a protein synthesis inhibitor and a phosphorylation inhibitor. All of these combinations were successful in activating horse oocytes. Although use of both a protein synthesis inhibitor and a phosphorylation inhibitor was 3-fold better than the protein synthesis inhibitor alone in this experiment, a calcium ionophore with a protein inhibitor was still sufficient for activating horse oocytes, albeit at 3-fold less efficiency than when combined with a phosphorylation inhibitor. Clearly, although a phosphorylation inhibitor may increase the efficiency of horse cloning, it is not critical.

Moreover, it would not have expected that it was necessary to increase the activation rate to 93.1%, in order to achieve success. Although an increase in activation rates might be expected to increase the efficiency of cloning somewhat, the efficiency could also be increased by simply increasing, for example doubling, the number of nuclear transfer oocytes. (*See* Declaration at ¶78.)

Second, the zona-free manipulation technique is not critical to successfully clone horses. Lagutina et al. (2005) found that the "zona-free method for embryo reconstruction proved very efficient in increasing the fusion rate and the efficient use of oocytes." (At 565-566, bridging paragraph.) Specifically, Lagutina et al. (2005) found that "the zona-free method is about 3.2 times more efficient than the zona-enclosed method in the case of cumulus-derived NT-embryos and 2.3 times more effective in the case of fibroblast-derived NT-embryos." (At 561-562, bridging paragraph.) Although the zona-free method may increase the efficiency of horse cloning, it is not critical.

As further evidence that the zona-free method is not required to clone horses, Woods et al. (2003), a copy of which is provided herewith, reports the cloning of a mule using horse oocytes. (At 1063, col. 1-2, bridging paragraph.) Woods et al. (2003) used oocytes with an intact zona. (Woods et al. (2003), Supporting Online Material at 3.) Since Woods et al. (2003) did not use the "zona-free" method, it is not critical for horse cloning.

Based on Woods et al. (2003) and Lagutina et al. (2005), the "zona-free" method is not required for cloning horses by somatic cell nuclear transfer. While it may increase the efficient utilization of oocytes, the use of more oocytes can compensate for this increase. (*See* Declaration at ¶78.)

Conclusion

The Board concluded that there was no reasonable expectation of cloning rabbits, mice, rats, and horses. (Decision at 50.) An error in the Board's analysis is the lack of evidence that the cited articles were using Campbell's teachings and failed to produce cloned mammals following the teachings of the specification. The Board's

argument is based on the ***successful*** cloning of the claimed species with procedures that may include additional, non-critical, variations of Campbell's procedures. This simply means that variations of Campbell's teachings are successful in cloning mammals. This does not mean that Campbell's teachings are insufficient.

Moreover, many of the variations used in the cited articles to appear to involve simply applying well-known techniques for rabbit and rat oocyte and embryo manipulation to cloning methodologies. For example, cloning rabbits appears to have involved little more than applying well-known techniques for *in vitro* manipulated rabbit embryos. Also, cloning of rats appears to have involved little more than applying well-known techniques for harvesting unactivated metaphase II rat oocytes.

The Board also relied on the fact that the cited articles were published in high profile journals as evidence that the results were non-routine. (Decision at 51-52.) The successful cloning of a mammal using a variation of Campbell's technique cannot negate enablement. Such results do not indicate that the employment of Campbell's technique was not routine.

The Board dismissed, as lacking any legal basis, Campbell's argument that the Examiner had not shown that repetition of the disclosed process would succeed eventually. (Decision at 50.) Applicant's argument has a legal basis, as set forth in the Brief. The principle is set forth by the Federal Circuit in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (1988). That principle is that mere repetition does not equate with undue experimentation. If all that is required for success is mere repetition of the disclosed process, Applicant's claims cannot require undue experimentation.

Applicant submits that this application is in condition for allowance. Should the Examiner disagree, she is invited to contact the undersigned to discuss any outstanding issues.

Respectfully submitted,

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